Laboratory of Personality and Cognition

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The fundamental scientific paradigm guiding research in the **Laboratory of Personality and Cognition (LPC)** is the analysis of individual differences. Few phenomena are more basic than the fact that human beings differ—in health, in rates of aging, in cognitive ability, in personality, in happiness, and in life satisfaction.

The Laboratory of Personality and Cognition (1) conducts basic and clinical research on individual differences in cognitive and personality processes and traits; (2) investigates the influence of age on these variables and their reciprocal influence on health, well-being and adaptation; and (3) employs longitudinal, experimental, and epidemiological methods in the analysis of psychological and psychosocial issues of aging, including health and illness, predictors of intellectual competence and decline, models of adult personality, and correlates of disease risk factors.

The Personality, Stress, and Coping Section conducts basic and applied research on personality as it relates to aging individuals including studies of stress and coping, mental and physical health risks and outcomes, adaptation and well-being. Basic research has centered on a taxonomic model of personality traits and its assessment.

The Cognition Section conducts studies that attempt to distinguish pathological from healthy, age-related cognitive changes in a broad range of cognitive tasks including short-term and long-term memory, visuo-spatial rotation, attention and decision tasks. In addition, structural and functional brain changes are examined using MRI and PET. Studies are performed on regional structural brain changes, especially the hippocampus, and their relationship to cognitive performance and dementia. Regional differences in cerebral blood flow derived from PET studies at rest and during cognitive challenge are related to aging and patterns of cognitive change.

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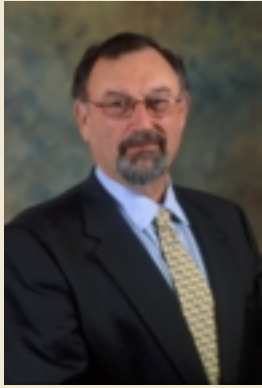
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Biography: Dr. Costa received his undergraduate degree in Psychology from Clark University and his doctorate in Human Development from the University of Chicago. After academic positions at Harvard and the University of Massachusetts at Boston, he joined NIA to inaugurate a Stress and Coping Section. Since 1985 he has been Chief of the Laboratory of Personality and Cognition. His research interests include adult development, personality assessment, and Alzheimer's disease.

Keywords:

personality assessment
Alzheimer's disease
five-factor model
personality
genetics

Recent Publications:

Trobst KK, et al. *J Pers* 2000; 68: 1233-1252.

McCrae RR, et al. *J Pers Soc Psychol* 2000; 78(1): 173-186.

Herbst JH, et al. *Am J Psychiatry* 2000; 157(8): 1285-1290.

A major obstacle to progress in personality psychology for many decades was the inability of psychologists to agree on a taxonomy of traits that would offer a comprehensive yet manageable set of trait constructs. Since 1983, this Laboratory has contributed to a worldwide consensus that the Five-Factor Model points to such a taxonomy. The broad factors of Neuroticism, Extraversion, Openness to Experience, Agreeableness, and Conscientiousness appear to encompass most specific traits, and offer a framework for systematic literature reviews and research designs.

Basic Research in Personality - The Five-Factor Model: One focus of research has been a comparison of the NEO-PI-R system with alternative operationalizations of the Five-Factor Model and alternative taxonomies. A popular psychobiological model has been proposed by C. Robert Cloninger and colleagues who assert that there are independent temperament dimensions corresponding to chemically-coded neural networks or brain systems: dopaminergic neurons regulate the dimension of novelty seeking, serotonergic neurons regulate harm avoidance, and norepinephrinergic neurons regulate reward dependence. At the biological level, they argue that the temperament traits are associated with neurochemical substrates that have a genetic basis. One implication of this theory is that genes associated with neurotransmitters should be related to the hypothesized temperament traits. Another implication is that traits hypothesized to have a shared genetic basis should covary at the phenotypic level. According to Cloninger and colleagues, the psychobiological model, as measured by the Temperament and Character Inventory (TCI), accounts for the genetic basis of the personality phenotype, whereas alternative models of personality like the five-factor model comprise genetically and environmentally heterogeneous factors. In a study of 946 male and female participants in the BLSA to whom the TCI was administered, 587 were genotyped for a polymorphism in the

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dopamine D4 receptor (D4DR) and 425 were genotyped for a polymorphism in the serotonin transporter (5-HTT) linked promoter region. Results indicated no significant association between D4DR polymorphisms and novelty seeking, and no significant association between 5-HTTLPR polymorphisms and harm avoidance. Furthermore, the factor structure of the TCI did not reveal the hypothesized phenotypic seven-factor structure. This study produced no support for the temperament and character model at either the biological or psychological level.

Personality Changes at Midlife: Past research has demonstrated high levels of stability of adult personality over long time intervals in men. However, few studies here or elsewhere have examined the long-term stability of personality of women; one of the exceptions (the Mills Longitudinal Study of about 100 women) reports appreciable change that invites replication. In collaboration with colleagues at the UNC Alumni Heart Study and Duke University Medical Center, a recently completed study on 495 women and 1,779 men in their 40's and retested after 6 to 9 years, tested hypotheses about the plateauing of rank-order stability and mean-level maturational changes in personality trait levels. Results confirmed previous longitudinal findings confirming basic stability for both women and men at the mid-life: rank-order stability coefficients were high, mean-level changes were small, and life events had only very specific influences on personality. Personality was shown to be resilient in that it was unchanged by the sheer occurrence of reported life events, whether positive or negative; but subjective appraisals of negative life circumstances did show limited effects on personality. Promising directions of future research suggest that events that affect central aspects of one's identity, such as loss of a job or changes in marital status, be a central focus. For both women and men, being fired from a job (vs. promoted) appears to increase Neuroticism (negative affect) and lower aspects of Conscientiousness. Effects of changing marital status differed for men and women: Divorce seemed to be liberating for women, but demoralizing for men.

Applied Research: Stress, Coping, and Psychopathology: Personality traits are important determinants of the ways in which people deal with stress. For example, Extraversion is associated with forms of coping that involve humor, talking about feelings, and seeking support; Agreeableness is associated with stoic and compliant attitudes in the face of stress. Our perspective integrates stress-and-coping research into the broader field of psychology, linked to normal adaptation, psychopathology, and the personality dimensions that affect all these. Traditionally, normal and abnormal psychology were held to be distinct and qualitatively different.

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Our research has shown that in many respects they are closely related, and thus that knowledge from one field is relevant to the other. For example, some of our research has focused on depression. We have shown that depressive symptoms are related to the normal personality disposition Neuroticism, can be predicted years in advance from personality traits, and can themselves predict psychiatric diagnoses noted in hospitalization records. Perhaps most important, we have also shown that depressive symptoms and the personality traits that predispose people to depression do not increase as a normal consequence of aging. Most older people are not depressed, and those that are should receive appropriate treatment.

Several studies have examined the potential of the five-factor model of personality to describe and differentiate various health risk behaviors among HIV and AIDS related patient groups. Perceived risk of contracting HIV has been theoretically and empirically linked to the likelihood of engaging in HIV risk behaviors; however, little is known regarding the determinants of risk perceptions and perceived risk of contracting HIV. A recent study examined the extent to which perceptions of risk are determined by HIV-related knowledge, history of engaging in HIV risk behaviors, and personality variables. Consistent with previous research from this laboratory linking low Openness to Experience (O) to defensive denial, individuals who engage in unsafe sex and deny any risk for contracting HIV had lower O scores than individuals who engage in unsafe sex and accept that they are at risk. Low O may facilitate minimization or even denial of risk as relatively closed individuals have difficulty imagining that these consequences apply to them and are closed to the feelings involved in dealing with a sense of vulnerability. Another study investigated how FFM personality traits are related to adherence to highly active anti-retroviral therapies (HAART) for HIV. Preliminary results suggest that individuals endorsing personality traits associated with high conscientiousness, openness and agreeableness report greater adherence to HAART; traits associated with neuroticism (e.g., depression) and extraversion (e.g., high excitement-seeking) were related to less than medically necessary adherence; and greater levels of angry hostility, lower gregariousness and lower positive emotions were associated with higher viral loads. These findings have direct implications for psychosocial interventions designed to sustain or improve adherence to HAART among HIV+ individuals.

Axis II of the DSM-IV is used for the diagnosis of personality disorders, which are defined as inflexible and maladaptive personality traits. It is reasonable to ask whether these traits are the same as or different from those encountered in non-psychiatric populations. Several recent studies on this question have concurred in finding strong and replicable links

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between scales measuring personality disorders and the five factors in both normal and clinical populations. The potential of the five-factor model of personality to describe and differentiate personality disorders was suggested by research in North American samples of patients and psychiatrically normal individuals. Relatively little research has examined relations between the FFM and personality disorders in psychiatric patient populations in other cultures. Former Visiting Scientist Dr. Jian Yang, in collaboration with investigators from the PSCS and the Hunan Medical University, conducted a multi-center study of over 2,000 psychiatric inpatients and outpatients throughout the People's Republic of China. Results showed that both personality traits and personality disorders can be reliably measured by Chinese translations of American instruments, and that the pattern of correlations between personality traits and disorders appears similar in China to that which has been reported in the US (cite). The results of these studies suggest that conceptions and measures of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) personality disorders are cross-culturally generalizable to Chinese psychiatric populations, and both personality disorders and personality traits may reflect biologically-based individual differences common to the human species as a whole. This is one of over 50 studies linking normal personal dimensions and personality disorders together they have led to a fundamental reconceptualization of the field of personality and psychopathology: Personality disorders do not correspond to discrete psychiatric entities, rather they are better construed as a systematic collection of problems in living associated with different dimensions of personality.

Collaborators: R. Michael Bagby, Ph.D., Jian Yang, M.D., Ph.D., University of Toronto; Krista K. Trobst, Ph.D., Jerry S. Wiggins, Ph.D., York University; Michael H. Bond, Ph.D., Chinese University of Hong Kong; Sampo V. Paunonen, Ph.D., University of Western Ontario; Gergorio H. del Pilar, Jean-Paul Rolland, Ph.D., University of Paris X Nanterre; Wayne D. Parker, Ph.D., Stephanie V. Stone, Ph.D., Peter Fagan, Ph.D., O. Joseph Bienvenu, M.D., Ph.D., Thomas Brashers-Krug, M.D., Gerald Nestadt, Ph.D., Johns Hopkins University; Fritz Ostendorf, Ph.D., Alois Angleitner, Ph.D., University of Bielefeld; Margarida P. de Lima, Ph.D., Antoino Simoes, Ph.D., University of Coimbra; Iris Marusic, Ph.D., Denis Bratko, Ph.D., University of Zagreb; Gian Vittorio Caprara, Ph.D., Claudio Barbaranelli, Ph.D., University of Rome; Joon-Ho Chae, Ph.D., Sogang University; Ralph L. Piedmont, Ph.D., Loyola College of Maryland; Mark R. Somerfield, Ph.D., American Society of Clinical Oncology; Thomas A. Widiger, Ph.D., University of Kentucky; Henry L. Masters III, M.D., AIDS Healthcare Foundation, Los Angeles CA; Neil Schneiderman, Ph.D., University of Miami.

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Biography: Dr. McCrae received a B.A. in Philosophy from Michigan State University, and a Ph.D. in Personality Psychology from Boston University. After three years at the Normative Aging Study in Boston, he joined the NIA to become Research Psychologist and Senior Investigator in the Personality, Stress, and Coping Section, Laboratory of Personality and Cognition. His work has been centered on studies of personality structure (the Five-Factor Model) and assessment (the Revised NEO Personality Inventory) and applications in health and aging.

Keywords:

personality structure
longitudinal studies
openness to experience
cross-cultural research

Recent Publications:

McCrae RR, et al. *Dev Psychol* 1999; 35: 466-477.

McCrae RR, et al. *J Pers Soc Psychol* 2000; 78: 173-186.

Personality traits are dimensions of individual differences in the tendencies to show consistent patterns of thoughts, feelings, and actions. Traits are important because their influence is pervasive: They affect personal interactions and social support, health habits and somatic complaints, attitudes and values, ways of coping, occupational and recreational interests, and much more. For the past 17 years, research in this laboratory has utilized a particular version of trait structure, the Five-Factor Model, and an instrument developed to assess 30 specific traits that define the five factors, the Revised NEO Personality Inventory (NEO-PI-R). Work in the past year has emphasized basic research on the generalizability of the model and its development in adulthood across cultures.

Cross-Cultural Studies of the Five-Factor Model: Cross-cultural studies are of immense importance in personality psychology, because the major variables thought to affect personality development—genetic inheritance, early family environment, and social structural variables such as class, political climate, and religious traditions—cannot feasibly or ethically be manipulated. Personality psychologists must depend on natural experiments, and many of these are provided by comparing individuals across cultures.

Since the publication of the NEO-PI-R in 1992, researchers outside the U.S. have translated the instrument into over 30 different languages, and many have collected data for their own research purposes. In collaboration with these investigators, we have recently conducted

cross-cultural studies of personality structure and development. In the first of these we reported an analysis of personality structure in Hong Kong Chinese and Japanese samples. Using statistical methods developed in part in this Laboratory, we showed that the Five-Factor Model is well replicated in both these non-Indo-European languages. Subsequent research has extended this finding to several other languages—in fact, to date no study using an authorized translation, adequate sample size, and appropriate analysis has failed to replicate the five-factor structure of the NEO-PI-R. These data suggest that the Five-Factor Model may be a human universal.

American studies of adult personality development can be summarized by saying that three of the factors (Neuroticism, Extraversion, and Openness) decrease, whereas the other two (Agreeableness and Conscientiousness) increase with age; most of the change occurs between age 18 and age 30. These cross-sectional differences might reflect cohort effects attributable to the historical experience of different generations of Americans. But other nations have had very different histories during the same period, and if age differences are due to cohort effects, it is unlikely that the same kinds of age differences would emerge in cross-sectional studies in those countries. However, reanalysis of data provided by collaborators in twelve countries (including Portugal, Russia, Turkey, Croatia, and South Korea) show very similar patterns of age differences, suggesting that these may perhaps best be interpreted as effects of intrinsic maturation.

In the first half of this century, anthropologists attempted to assess the modal personality of various groups and relate personality to features of culture. In an updating of this endeavor, recent analyses have examined the mean levels of personality traits across cultures. Preliminary results suggest that personality profiles obtained in different languages or versions are comparable to the original, that subgroups (men and women, students and adults) from the same culture have similar personality profiles, and that culture-level analyses of personality traits show the same Five-Factor structure seen in analyses at the individual level.

The Origins of Personality - Behavior Genetics: According to Five-Factor Theory, personality traits are endogenous basic tendencies. Genetic factors are expected to play a major role in their origin and development, whereas environmental factors like culture should play a minor role. In collaboration with Swedish researchers, we published one of the first studies on the heritability of Openness to Experience, and we collaborated

with John Loehlin and Oliver John to reanalyze the classic National Merit Twin Study data for all five factors. A collaboration with behavior geneticists in Canada and Germany suggests that the five factors are strongly heritable in both these two cultures. In addition, that study demonstrates that more narrow and specific facet-level traits are also substantially heritable. Thus, it appears that there is a genetic basis for many of the details of personality, as well as the broad outlines.

Genetic covariance analyses are used to examine the origins of covariation between traits. In previous research, it has been claimed that the phenotypic structure is unaffected by shared environmental influences, but is mirrored by both genetic influences and non-shared environmental influences. However, non-shared environmental influences are estimated as a residual term that includes measurement bias. When we supplemented Canadian and German twin data with cross-observer correlations from American samples, measurement bias was reduced, and the phenotypic structure appeared to be due only to genetic influences.

Studies of Openness to Experience: Openness to Experience is the least well understood of the five personality factors. Different versions of the factor have been labeled Culture, Inquiring Intellect, Imagination, and Independence of Judgment. As assessed by the NEO-PI-R, Openness is seen in Fantasy, Aesthetics, Feelings, Actions, Ideas, and Values, and is thus much broader than labels such as Intellect suggest. Correlational studies in the BLSA have shown that Openness is empirically related to a wide variety of constructs, including Jung's Intuition, Hartmann's Thin Boundaries, Tellegen's Absorption, and Murray's Need for Sentience, as well as to corresponding factors in alternative measures of the Five-Factor Model (e.g., Goldberg's Intellect). It shows smaller, if still significant, correlations with measures of intelligence and divergent thinking ability.

This body of empirical findings has been used to develop a conceptualization of Openness with both motivational and structural aspects. Although Openness is essentially a matter of differences in the internal processing of experience, it has far-reaching consequences in social interactions. A review of the literature showed that Openness or related constructs were important for understanding cultural innovation, political ideology, social attitudes, marital choice, and interpersonal relations.

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Biography: Dr. Thayer received a B.A. in Psychology from Indiana University, and Master's and Ph.D. degrees from New York University. After academic positions at Penn State University and the University of Missouri, he joined NIA to initiate a program on Emotions and Quantitative Psychophysiology. His research interests concern biological and psychological adaptation and flexibility in the context of dynamical systems models with applications to psychopathology, pathophysiology, and health. This work utilizes indices of autonomic nervous system function derived from cardiac variability measures to probe whole organism systems.

Keywords:

heart period variability
spectral analysis
anxiety

Recent Publications:

Thayer JF, et al. *Psychophysiology* 2000; 37: 361-368.

Uijtdegaage SH, et al. *Clin Auton Res* 2000; 10: 107-110.

Heart Period Variability as an Index of Neurovisceral Integration: One aspect of our research program is to develop, elaborate, and apply a model of neurovisceral integration in the context of normal and pathological functioning. This model uses heart period variability (HPV) to index the functioning of central-peripheral feedback mechanisms that produce goal-directed behavior. We have related HPV to attentional regulation and affective regulation in humans. These studies suggest that autonomic, attentional, and affective regulation are coordinated in the service of system adaptability and goal-directed behavior.

Autonomic Characteristics of Anxiety and Mood Disorders: Anxiety and depression are disorders associated with somatic symptoms such as tachycardia, rapid breathing, and disturbed sleep. Moreover, anxiety and depression are risk factors for cardiovascular morbidity and mortality. Our research has focused on the autonomic characteristics on these disorders to investigate their physiological and psychological concomitants with an eye toward understanding their development, course, and treatment. Research to date indicates that these disorders are associated with a relative decrease in vagally mediated cardiovascular control. This lack of cardiac vagal control is associated with poor affective and attentional regulation. Importantly, these deficits normalize with therapeutic intervention.

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Cardiovascular Variabilities and Health: We are examining the relationship between HPV and cardiovascular system control. This research suggests that HPV and blood pressure variability (BPV) are inversely related in the healthy, intact organism and serves to maintain adequate blood pressure control. In spinal cord injury, the relationship between HPV and BPV can become dysfunctional, leading to poor blood pressure regulation and increased risk for cardiovascular disorders.

Collaborators: Thomas D. Borkovec, Penn State University; Jos F. Brosschot, University of Leiden, The Netherlands; Bruce H. Friedman, Virginia Tech University; Arve Asbjornsen, Kenneth Hugdahl, Bjorn Helge Johnsen, Jon Christian Laberg, University of Bergen, Norway; Richard D. Lane and Geoffrey L. Ahern, University of Arizona; Richard A. Tyrrell, Clemson University.

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Biography: Dr. Zonderman received his undergraduate degree in Behavior Genetics from University of Massachusetts and his doctorate in Psychology from the University of Colorado. After a postdoctoral fellowship in multivariate statistics at the University of California, Berkeley, and academic positions at University of California, Davis and The Johns Hopkins University, he joined NIA as a Senior Staff Fellow in the Stress and Coping Section. Since 1997, he has been Chief of the Cognition Section in the Laboratory of Personality and Cognition. His research interests include individual differences in cognition and personality and their relationship with adult morbidity and mortality, predicting the onset of cognitive impairments and Alzheimer's disease, and the role of genetics in cognitive declines and personality.

Keywords:

individual differences
age-associated cognitive decline
mild cognitive impairment
risk factors and protective factor for AD
cognitive decline and Alzheimer's disease
behavioral genetics

Recent Publications:

Kawas C, et al. *Neurology* 2000; 54: 2072-2077.

Resnick SM, et al. *Cereb Cortex* 2000; 10: 464-472.

Maki PM, et al. *Am J Psych* 2000; In press.

Moffat SD, et al. *Neurology* 2000; 55: 134-136.

Moffat SD, et al. *Arch Int Med* 2000; 160: 2193-2198.

Distinguishing Pathological from Normal Cognitive Aging: Research in the Cognition Section focuses on distinguishing pathological from normal cognitive aging. The purpose of this research is to identify predictors of cognitive morbidity, and to identify which cognitive processes are preserved with aging and which processes are vulnerable to disease. The primary effort of research in the Cognition Section is focused on longitudinal research in the Baltimore Longitudinal Study of Aging (BLSA). Cognitive tests have been administered to participants in the BLSA since 1960. Some individuals presently in the study have as many as seven repeated assessments beginning in the 1960's.

The cognitive tests administered to participants in the BLSA reflect our primary interest in pathological cognitive impairments, especially Alzheimer's disease (AD). The cognitive testing program is divided into two batteries, one for longitudinal prediction and another for cognitive and neuropsychological outcomes. The longitudinal repetitions of these tests distinguish typical changes in performance associated with aging from changes in performance which may be associated with disease when combined with neurological and neuropsychological outcomes and clinical diagnoses of AD.

An increasingly important area of research in the Cognition Section focuses on factors that reduce the risk of cognitive declines. An example of this focus is the finding that nonsteroidal anti-inflammatory drugs reduce the risk of Alzheimer's disease. Another example of this focus is based on recent findings that estrogen replacement therapy reduces the

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risk for both AD and cognitive declines in post-menopausal women. In an intervention study testing the effects of hormone replacement on cognition, we are examining the effects of estrogen and testosterone in older women and men in conjunction with structural and functional neuroimages.

Cognitive Declines in Aging Subjects Free of Dementing Diseases: In people with no signs of dementia, some cognitive abilities resist decline while other abilities show characteristic age-related changes beginning in the 50's or 60's. Research by investigators in the Cognition Section has shown that vocabulary scores generally resist declines, and may increase slowly over time until there are small decreases after the eighth or ninth decades. Immediate visual memory shows a much different pattern of change. We found that errors in immediate visual recall increased exponentially with increased age in both cross-sectional and longitudinal analyses.

We also found that there were different rates of change in separate types of errors over time. Distortions, rotations, perseverations and mislocations were the most frequent errors across all ages. Although older participants made significantly greater errors regardless of error type, the greatest age differences were found for distortions and omissions. Men and women showed similar patterns of age-associated increases in errors, but there was a significant interaction between gender and error type indicating that women across all ages made more omissions and rotations, not other types of errors. Longitudinal analyses showed that distortions, omissions and rotations increased with age. Although women made more omission errors, men showed steeper increases with age.

Long-Term Predictions of Cognitive Impairment and Dementia: The onset of cognitive impairment is either a discrete event or a gradual process that manifests over time. We asked whether changes in previous test performance predict evidence of cognitive impairment assessed by the Mini-Mental Status Examination (MMSE) over relatively long intervals. We hypothesized that visual memory administered prior to the MMSE would significantly account for cognitive impairment after controlling for age at mental status exam and vocabulary score (a measure highly related to general intelligence). The correlations between visual memory and MMSE over 6-8 and 9-15 years were .36 and .34 ($p < .05$). These results provide preliminary evidence that mental status can be predicted, at least in part, by earlier performance on cognitive tests. Although the present findings are limited to only these cognitive tests, they provide important evidence that early signs of dementia may be detectable as many as 6-15 years prior to noticeable decline on mental status tests.

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Six-year changes in immediate visual memory predicted Alzheimer's disease (AD) prior to its onset. Individuals with diagnoses of AD had larger changes in immediate memory performance over the six-year interval prior to the estimated onset of their disease than subjects without AD. Six-year longitudinal change in immediate visual memory performance also predicted subsequent cognitive performance 6-15 and 16-22 years later, even after adjusting for the influences of age, general ability, and initial immediate memory. These results provide evidence that change in immediate visual memory performance has long-term prognostic significance. These results further suggest that change in recent memory performance may be an important precursor of the development of the disease.

Analyses comparing BLSA participants who developed dementing illnesses with nondemented participants also showed that particular errors in visual memory may be more sensitive markers of impairment than others. More than 5 years before the onset of illness, demented individuals made more distortion errors than participants who did not develop dementing illnesses. In addition, individuals with signs of dementia had significantly greater rates of change in perseverations, rotations, and size errors compared with nondemented participants. These findings suggest that immediate visual memory is an important test for distinguishing normal from pathological cognitive decline and that specific types of errors in short-term memory may be important early markers of dementia.

Risks and Protective Factors for Cognitive Decline: If cognitive decline is an important predictor of pathological cognitive aging then it seems reasonable to investigate factors that decrease or increase the risk of cognitive decline. Estrogen replacement therapy (ERT) is increasingly recommended for postmenopausal women due to its potential beneficial effects on physical health in older women. The possibility of a protective effect on cognitive function has also been suggested. In the BLSA, women receiving hormone treatment at the time of testing made significantly fewer errors in immediate visual recall than women who were not on hormone therapy. Less memory change was found in women who started hormone therapy between examinations than women who never received hormone therapy. These findings support the notion that estrogen has a beneficial role on cognitive functioning in aging women.

We continue to extend our present studies on the risks and protective factors for cognitive declines and dementias. In particular, as we gather additional repeat data on which to base reliable measures of cognitive trajectories, we will relate apoE and other genotypic and genomic

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measures to determine whether there are critical periods of decline. In addition, we will examine the role of modulators of cognitive decline such as hypertension and hormone replacement therapy, particularly in conjunction with MRI anatomical and PET functional assessments. We will also examine chronicity of hypertension, adequacy of blood pressure control, and differential effects and interactions with other known risks such as apoE genotype.

Collaborators: Dr. Keith Whitfield, Pennsylvania State University; Dr. Shari Waldstein, University of Maryland Baltimore County; Dr. Katherine Tucker, Tufts University.

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Biography: Dr. Resnick received her Ph.D. in Differential Psychology and Behavioral Genetics from the University of Minnesota and completed a postdoctoral fellowship in Neuropsychology and Neuroimaging at the University of Pennsylvania. She was Research Assistant Professor of Psychology in Psychiatry at the University of Pennsylvania prior to joining the Laboratory of Personality and Cognition, NIA in 1992. She studies brain-behavior associations in health and disease and is currently the principal investigator of the brain imaging component of the Baltimore Longitudinal Study of Aging (BLSA). This longitudinal neuroimaging study focuses on early structural and physiological brain changes that may be predictors of memory and cognitive change in older individuals. Through this study and others in the BLSA, she has also been examining the hormonal modulation of age-associated cognitive and brain changes.

Keywords:

memory aging
Magnetic Resonance Imaging
Positron Emission Tomography
estrogen and cognition

Recent Publications:

Resnick S, et al. *Cereb Cortex* 2000; 10(5): 464-472.

Maki PM, et al. *Neurobiol Aging* 2000; 21(2): 373-383.

Brain Changes as Predictors of Cognitive and Memory Decline: The goal of our research program is to identify brain changes which may predict declines in memory and other cognitive functions in older individuals. We use magnetic resonance imaging (MRI) to measure the structure of the brain and positron emission tomography (PET) to measure changes in regional cerebral blood flow (rCBF) during the performance of memory tasks and over time. A variety of risk and protective factors for cognitive impairment and dementia are examined.

Early Markers of Alzheimer's Disease - Brain Changes in the Baltimore Longitudinal Study of Aging (BLSA): We are performing a longitudinal neuroimaging study involving annual MRI and PET scans and neuropsychological evaluations in selected BLSA participants aged 55 and older. This longitudinal design provides a sensitive to way to investigate the relationship between changes in brain structure and physiology and decline in memory and cognition. Furthermore, using the wealth of prior psychological and medical information available for BLSA participants, we are able to examine trajectories of cognitive aging in relation to individual differences in the brain years later. To date, approximately 155 individuals (90 men, 65 women) have enrolled in the brain imaging study and most have completed their fifth neuroimaging assessment.

The specific goals of this study are: to determine the rate of brain changes with age, including increases in brain atrophy and ischemic/demyelinating white matter abnormalities; to determine the association between trajectories of memory and cognitive change and changes in brain structure and function; and to determine whether risk and protective factors, such as genetic susceptibility factors, hormone replacement therapy, use of non-steroidal anti-inflammatory agents, and vitamins, modulate these relationships. An understanding of the associations between brain and neuropsychological changes, as well as early detection of these changes, will be critical in identifying individuals likely to benefit from new interventions in preventing and treating Alzheimer's disease and other memory problems in the elderly.

MRI data from the first 2 years of our longitudinal brain imaging study have been published. A great deal of effort in our laboratory has focused on the development and validation of an image processing approach that provides sufficient accuracy for longitudinal studies. Quantitative analysis of MRI volumes, including separate estimates of gray and white tissue volumes and cerebrospinal fluid (CSF), for 116 subjects who have completed 2 evaluations reveals significant effects of age and sex on brain volumes and ventricular volumes. The cross-sectional findings from the Year 1 MRI scans indicate less gray and white matter volume and more ventricular CSF in older compared with younger participants; the magnitude of these findings is different across frontal, parietal, temporal and occipital brain regions. Consistent with previous studies, men have greater ventricular CSF volumes. There are no detectable changes in lobar brain volumes over a one-year period, but there was a small but significant increase in the volume of the ventricles.

We have also examined the effect of Apolipoprotein E genotype on hippocampal volumes and rates of longitudinal hippocampal volume loss. Neuroimaging study participants without dementia who carry the e4 allele (e4+) did not differ from those negative for the e4 allele (e4-) at initial evaluation. In contrast, e4+ individuals showed a faster rate of hippocampal volume loss than age, sex and education matched e4- individuals. Because both the presence of the e4 allele and hippocampal volume loss are risk factors for Alzheimer's disease (AD), our findings suggest one mechanism by which e4 genotype may confer an increased risk for AD.

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In addition to morphologic predictors of cognitive impairment and AD, we are investigating the utility of early blood flow changes as predictors of cognitive and memory change. PET-rCBF studies are performed annually as part of our BLSA neuroimaging study. These scans are obtained under three conditions: during rest and the performance of verbal and figural delayed recognition tasks. This procedure is conceptualized as a cognitive stress test to examine age-associated changes in rCBF during increased demand. Our memory tasks produce robust patterns of CBF activation, with increased blood flow in prefrontal cortex (right > left), bilateral insula and visual association areas during memory recall. In addition, voxel-based maps of the associations between age and resting rCBF (normalized for global CBF) demonstrate significant negative correlations between age and CBF in the insular and superior temporal regions, and in visual association cortex (Areas 18 and 19) bilaterally for both men and women. To our knowledge, this sample represents the largest study of associations between age and regional CBF studied with PET and provides a detailed map of age differences in blood flow during a period of accelerating cognitive and memory decline.

Effects of Hormones on Cognitive Decline:

Hormone Replacement Therapy: A major focus of our research program is the investigation of the potential modulatory role of hormone replacement therapy on risk for Alzheimer's Disease and cognitive and memory decline in older women. We have shown that women in the BLSA who had ever used estrogen replacement therapy had a reduced risk of developing Alzheimer's Disease in comparison with women who had never used hormone therapy. We have also shown that nondemented women in the BLSA who were using estrogen replacement therapy performed better on a test of short-term memory for designs compared with never-users. In a small subgroup of women with memory assessments prior to and following initiation of hormone treatment, the estrogen therapy appeared to protect against age-associated decline in memory. We have also compared ERT users and nonusers who participate in our longitudinal imaging study. ERT users and nonusers showed significant differences in the patterns of brain activation during the performance of memory tasks. Most recently, we reported that ERT users compared with nonusers showed greater relative increases over a 2 year period in CBF in the hippocampus, entorhinal cortex, posterior parahippocampal gyrus, and portions of the temporal lobe. Interestingly, these regions overlap substantially with those showing physiologic abnormalities in early AD and in individuals at increased genetic risk for AD.

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As our published studies to date have been observational and relied on women who choose to take estrogen as part of their regular medical care, we have initiated an ancillary study to the Women's Health Initiative randomized clinical trial. This study, the Women's Health Initiative Study of Cognitive Aging (WHISCA), examines the effects of hormone replacement therapy on longitudinal change in memory and other cognitive functions within the context of the large randomized intervention trial.

DHEA and Cognition: Dehydroepiandrosterone (DHEA) is a widely available hormone marketed as an anti-aging dietary supplement beneficial for physical and cognitive health. We have examined the associations of plasma concentrations of DHEA sulfate (DHEAS) and longitudinal changes in DHEAS with cognitive changes in older men in the BLSA. In this large sample, there were no associations between DHEAS concentrations or longitudinal changes in DHEAS and multiple measures of cognitive change. These data offer no support for the hypothesized relationship between endogenous DHEA levels and cognitive health.

Future Directions: Our future work will emphasize continuation of the longitudinal neuroimaging study, including continued acquisition of annual evaluations, further analyses of existing imaging and neuropsychological data, development of new approaches for longitudinal analyses of functional images, and examination of modulating factors on the relationship between brain and neuropsychological changes. The data collected over the first 2 years of the study indicate only small changes over one year in regional brain volumes and ventricular CSF. In contrast, the cross-sectional age differences between younger and older participants are 5 to 7% in frontal and temporal volumes and 51% in ventricular volume. It will be critical to continue repeated evaluations to examine the relation between brain and cognitive changes as the number of individuals with cognitive decline increases over the duration of the study.

Another important area of future research, which has only recently received attention in the brain imaging literature, is the role of modulatory factors on brain morphology and function. We are examining suggested risk and protective factors in relation to brain changes, neuropsychological changes and their association. For example, data on family history for Alzheimer's disease, apolipoprotein E genotype, head trauma, history of hypertension, use of estrogen replacement therapy, and circulating

hormones (DHEA, testosterone, cortisol) are being investigated as potential modulators of the relationship between brain and neuropsychological changes. The neuroimaging study has been expanded to younger adults to determine whether our observations of sex differences in the brain reflect group differences or differential aging for men and women. Ongoing and future work will include intervention studies to examine suggested protective agents, such as estrogen and testosterone, on brain structure and function. In collaboration with Dr. Pauline Maki, we are performing studies of regional brain morphology and functional activity within the context of double-blind placebo-controlled studies of estrogen and testosterone effects on cognition and mood in older women and men, respectively.

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Biography: Dr. Maki received her Ph.D. in Experimental Psychology from the University of Minnesota and completed a postdoctoral fellowship in the Dementias of Aging at Johns Hopkins University School of Medicine. Following her postdoctoral fellowship, she held joint appointments as a National Research Council (NRC) Fellow in the Laboratory of Personality and Cognition, NIA and as an Instructor in the Department of Psychiatry and Behavioral Sciences at Johns Hopkins. In 1999, she joined the Laboratory as an Investigator. She studies the neuropsychology of memory and the effects of hormone replacement therapy on memory, other cognitive abilities, and brain functioning. She leads a number of clinical intervention trials that focus on the effects of estrogen, selective estrogen receptor modulators (SERMs), and testosterone on cognition and brain functioning in older adults.

Keywords:

estrogen
cognition
hormone
memory
brain activation

Recent Publications:

Maki PM, et al. *Am J Psych* 2000; In press.

Maki PM, et al. *Neurobiol Aging* 2000; 21: 373-383.

Effect of Sex Steroid Hormones on Cognition and Brain Functioning: The effect of aging on cognition and brain functioning varies from one individual to the next. Recent studies suggest that one of the factors influencing individual differences in cognitive aging is the use of hormone replacement therapy (HRT). For example, recent findings from the Baltimore Longitudinal Study on Aging (BLSA) suggest that the use of estrogen replacement therapy (ERT) protects against age-associated declines in memory and against the development of Alzheimer's disease. One limitation of such studies is that the women who participated in them elected on their own to receive ERT. Research suggests that such women tend to be better educated and to receive better health care than women who do not receive ERT. The bias is termed the "healthy user effect."

To address this bias, we are recruiting postmenopausal women who are not currently receiving hormone replacement therapy, and we are investigating their cognitive functioning at two points, after receiving ERT for 3 months and after receiving placebo for 3 months. We are conducting a parallel study on men, age 65 and older. Men experience a gradual loss of testosterone, about 1% a year after age 40. Little is known about how testosterone replacement therapy affects cognition in older men, though there is some suggestion that the hormone may enhance spatial abilities. Both studies examine both cognitive test scores and neuroimaging outcomes. We use positron emission tomography (PET) to examine brain functioning and magnetic resonance imaging (MRI) to examine brain structure.

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The overall aim of the study is to determine whether estrogen and testosterone enhance cognitive functioning and mood in healthy older adults, and to identify the neural correlates of the expected changes. By studying the same woman on and off of ERT, we can extend our previous findings to all women, not just those who typically choose to go on ERT. By overcoming the healthy user bias of previous studies, we can more strongly support the hypothesis that ERT improves memory and verbal abilities in women. Moreover, by extending this area of inquiry to the study of testosterone replacement, we can begin to address whether HRT offers similar benefits to men.

Finally, to address the healthy user bias in the context of a large-scale randomized clinical trial, we recently initiated the Women's Health Initiative Study of Cognitive Aging or WHISCA, a 6-year longitudinal study assessing cognitive outcomes in 2900 women assigned randomly to receive active treatment (estrogen replacement therapy or estrogen and progesterone) or placebo. WHISCA is an ancillary study to the Women's Health Initiative (WHI) Randomized Hormone Replacement Trial and is the largest randomized trial of hormone replacement therapy on cognitive outcomes. WHISCA will provide invaluable data on the effects of hormone treatments on cognitive aging.

Effects of Endogenous Estrogens on Cognition: Reproductive events such as menarche, pregnancy, and menopause influence a woman's risk for a number of diseases. For example, the incidence of breast cancer is higher in women who have longer estrogen exposure due to early menarche, late menopause, or nulliparity. Conversely, a naturally high exposure to estrogen over a lifetime may decrease the chance of developing osteoporosis. Little is known about the effects of endogenous estrogens on cognition across the lifespan. We are currently examining this in the BLSA cohort and in other cohorts.

Natural fluctuations in ovarian hormones across the menstrual cycle allow for noninvasive studies of the effects of estrogen on cognition in young women. Studies indicate that fluctuations in estradiol underlie a reliable pattern of cognitive change across the menstrual cycle. Increases in estrogen are associated with improvements on tests in which women typically outperform men such as verbal fluency and decreases on tests in which men typically outperform women such as mental rotations. We are examining cognitive function in women across the menstrual cycle to see if the effects of endogenous estrogen in young women are similar to the effects of exogenous estrogen (i.e., estrogen replacement therapy) in older women.

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Effects of Selective Estrogen Receptor Modulators (SERMs) on Cognition and Brain Functioning: We recently extended our research on hormones and cognition to a newer class of estrogen agents, selective estrogen receptor modulators (SERMs). SERMs have mixed estrogen agonist-antagonist properties, acting as agonists on bone and antagonists on certain reproductive tissues. The two most commonly prescribed SERMs are tamoxifen and raloxifene. There have been no observational or clinical intervention trials comparing the effects of tamoxifen and raloxifene on cognition, nor any observational or clinical intervention studies comparing the effects of SERMs and common HRT regimens on cognitive aging. The effect of tamoxifen on cognition is unknown, and the only published study on the effects of raloxifene on cognition showed a small, transient benefit to memory. Such studies take on great importance, because raloxifene is being offered as an alternative to HRT and tamoxifen is being recommended for primary prevention of breast cancer in women who have only a moderate increase in risk for this disease. If one or both of these SERMs act as estrogen agonists in brain, they may be beneficial to cognitive functioning. In contrast, if one or both act as antagonists, they may be detrimental to cognitive functioning. In the face of potential widespread use of SERMs in healthy women, information on the effects of these agents on memory and other cognitive functions is essential.

To better understand the effects of SERMs on cognition and brain functioning, we are conducting a series of observational and clinical trials. One clinical trial examines the effects of tamoxifen on cognition and brain functioning in women with breast cancer. Another clinical trial examines and compares the effects of tamoxifen, raloxifene, and estrogen on cognition and brain functioning in healthy postmenopausal women. We are conducting parallel observational studies that involve women who take tamoxifen for prevention of breast cancer and women who take raloxifene for prevention of osteoporosis. Finally, we are conducting an ancillary study to the National Cancer Institute initiated the Study of Tamoxifen and Raloxifene (STAR), a multi-center, 5-year, randomized clinical trial comparing the two drugs in 22,000 women at increased risk for breast cancer. The ancillary study, called STAR-Cog, will involve neuropsychological assessments in 1800 STAR volunteers, age 65 and older, randomly assigned to raloxifene or tamoxifen. The aims of the study are to address the long-term effects of raloxifene and tamoxifen on cognitive aging and the long-term cognitive effects of tamoxifen and raloxifene in comparison to those of ERT and ERT + progesterone.

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